

REVIEW

Primary Sjögren's syndrome: new clinical and therapeutic concepts

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Sicca features are the central clinical manifestations of Sjögren's syndrome (SS), but recent studies have confirmed that primary SS has a systemic expression, including extraglandular manifestations. Patients with a predominantly extraepithelial expression should be managed differently from patients with predominantly periepithelial or sicca limited disease. In coming years treatment will be based on muscarinic agonists for sicca features and immunosuppressive/biological agents for extraglandular features.

prognosis and outcome of patients with primary SS.

"Cutaneous vasculitis is significant in the prognosis and outcome of patients with primary SS"

Patients with primary SS may also present a wide range of non-vasculitic lesions.⁴ One of the most characteristic are polycyclic, photosensitive cutaneous lesions, previously reported in Asian patients with primary SS (annular erythema) and recently described in white patients.^{4,7,8} These lesions are clinically identical to those seen in patients with subacute cutaneous lupus erythematosus, suggesting a common cutaneous disease (closely related to anti-Ro/SSA antibodies) in patients with either primary SS or systemic lupus erythematosus (SLE). Table 1 summarises other cutaneous processes which have been described in patients with primary SS.^{7–15}

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lachrymal glands.¹ In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary SS. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy)² to a systemic process with diverse extraglandular manifestations.³ An increasing number of SS related publications in the past 5 years have contributed to a better understanding of the systemic involvement and the outcome of the disease. Advances in the treatment of sicca and extraglandular features are especially noteworthy. This review summarises recent work focused on extending and characterising the extraglandular involvement of primary SS and evaluating new therapeutic approaches.

CUTANEOUS INVOLVEMENT

Cutaneous features are considered one of the most characteristic extraglandular manifestations of primary SS. A recent study has described a wide spectrum of cutaneous lesions in patients with primary SS, with vasculitis being detected in 10% of patients.⁴ The main characteristic of SS associated cutaneous vasculitis in that study was the overwhelming predominance of small (leucocytoclastic) versus medium vessel vasculitis, with life threatening vasculitis being closely related to cryoglobulinaemia. Other authors have demonstrated the association of cutaneous purpura with lymphoma development and mortality.^{5,6} Taken together, these studies show the clinical significance of cutaneous vasculitis in the

PULMONARY INVOLVEMENT

Various studies have recently described the predominance of bronchial/bronchiolar involvement rather than interstitial disease.^{16,17} Franquet *et al* described bronchiolar abnormalities in one third of their patients, with a higher frequency of air trapping in lower lobes.¹⁸ Papiris *et al* described small airway disease as the main functional disorder,¹⁹ and Taouli *et al* found that large and/or small airway disease was the predominant computed tomography scan pattern in more than 50% of their patients.²⁰ The results of pulmonary functional tests often correlated with the computed tomography scan pattern, although no correlation was found in some cases,²¹ suggesting the need to combine both diagnostic procedures in patients with suspected pulmonary disease. Subsequent diagnostic procedures may include bronchoscopy with bronchioalveolar lavage and transbronchial biopsy.^{19,22} The natural history of pulmonary involvement in primary SS was demonstrated by Davidson *et al*, who found that although lung disease usually occurred early in the course of SS (predominantly in Ro+ patients), most of these patients

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Abbreviations: ANA, antinuclear antibodies; CNS, central nervous system; ESR, erythrocyte sedimentation rate; GMN, glomerulonephritis; IFN α , interferon α ; PSN, pure sensory neuropathy; RA, rheumatoid arthritis; RP, Raynaud's phenomenon; SHL, sensorineural hearing loss; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic sclerosis; TIN, tubulointerstitial nephritis

Table 1 Cutaneous involvement of patients with primary SS

<i>a) Cutaneous vasculitis</i>
SS associated small vessel vasculitis ⁴
Cryoglobulinaemic vasculitis
Urticarial vasculitis
Other leucocytoclastic vasculitis
SS associated medium vessel vasculitis ^{4, 9}
<i>b) Other cutaneous processes</i>
Ro associated, polycyclic, photosensitive cutaneous lesions ^{7, 8}
Erythema nodosum ⁴
Livedo reticularis ⁴
Thrombocytopenic purpura ⁴
Lichen planus ⁴
Vitiligo ⁴
Nodular vasculitis ^{4, 10}
Cutaneous amyloidosis ^{4, 11-14}
Annular granuloma ⁴
Granulomatous panniculitis ¹⁵

did not develop a progressive pulmonary disease.²³ Clinically, the frequency of bronchial/bronchiolar disease in patients with SS with pulmonary involvement shown by several studies, and the slow progression and insidious clinical course often seen in these patients, should be borne in mind.

VASCULAR INVOLVEMENT

Raynaud's phenomenon (RP) is probably the most common vascular feature seen in primary SS, with a prevalence of 13%.²⁴ The clinical significance of RP in patients with primary SS is twofold. On the one hand, RP may be the first feature seen in some patients, suggesting a diagnosis of primary SS. On the other hand, RP may identify a specific subset of patients having positive immunological markers suggestive of systemic sclerosis (SSc).

"Raynaud's phenomenon is often the first feature seen in SS but may also suggest the presence of limited SSc"

In this latter group, a specific search for anticentromere antibodies should be performed, especially when high titres of antinuclear antibodies (ANA) with negative anti-Ro/La antibodies are present.²⁴⁻²⁶ This clinico-immunological subset of patients with SS, RP, and anticentromere antibodies need a closer follow up, paying special attention to the development of an associated limited form of SSc. These patients should be considered as having SS associated with SSc rather than SS "secondary" to SSc, as Manoussakis *et al* have suggested for the case of coexisting SS and SLE.²⁶

Table 2 Renal disease in patients with primary SS: altered renal parameters and renal biopsy results

	No	Total No of patients	%
<i>Altered renal parameters²⁷⁻²⁹</i>			
Proteinuria	55	198	28
Distal RTA	31	237	13
Low creatinine clearance	29	182	16
<i>Renal biopsy^{29, 30}</i>			
Tubulointerstitial nephritis	16*	27	59
Glomerulonephritis	12*	27	44
Membranoproliferative*	6†	12	50
Mesangial proliferative*	5	12	42
Membranous*	1	12	8

*One patient had coexisting tubulointerstitial nephritis and glomerulonephritis; †five patients had associated cryoglobulinaemia.

RENAL INVOLVEMENT

Although renal disease in patients with primary SS has usually been considered as predominantly tubular, several studies have described glomerulonephritis (GMN) in a substantial percentage of patients with primary SS and renal disease²⁷⁻³⁰ (table 2). Of the 27 patients with SS with documented renal biopsy, 15 patients showed tubulointerstitial nephritis (TIN), 11 GMN, and one had both entities. In these patients,^{29, 30} the most common glomerular diseases were membranoproliferative GMN in seven patients, mesangial proliferative GMN in six, and membranous GMN in two. Cryoglobulinaemia was detected in half of the patients and only two finally developed chronic renal failure requiring haemodialysis.

These two types of SS related renal disease (tubular and glomerular) have important pathogenic, clinical, and prognostic implications. TIN is considered to be a specific tubular epithelitis that is usually found in younger patients, and is characterised by an indolent subclinical course without development of renal failure. In contrast, GMN should be considered a severe extraepithelial manifestation closely associated with cryoglobulinaemia and hypocomplementaemia, appearing late in the course of primary SS and associated with higher morbidity and mortality.³⁰ A renal biopsy is probably unnecessary in patients with a suspected TIN, while those with GMN require early diagnosis and therapeutic management.

NEUROLOGICAL INVOLVEMENT

Although earlier studies described central nervous system (CNS) involvement as a common extraglandular manifestation of primary SS, symptomatic CNS involvement is rarely found in large published series.^{3, 5, 31, 32} Evaluation of the clinical significance of CNS features in patients with primary SS is difficult owing, on the one hand, to the broad spectrum of both CNS and psychiatric processes that may be seen and, on the other hand, to the possible epidemiological overlap between SS and various CNS processes often observed in older patients, such as cerebrovascular disease, Alzheimer's disease, or multi-infarct dementia. An illustrative example is the clinical significance of the white matter lesions detected in asymptomatic, older patients with primary SS.³³ These lesions are often seen in control groups matched for age and sex and are also known to increase with age.³⁴ Various studies have described other CNS processes in patients with SS^{33, 35-47} (table 3).

Pure sensory neuropathy (PSN) is recognised as a characteristic neurological complication of primary SS caused by damage of the sensory neurones of the dorsal root and gasserian ganglia. New research has described three differentiated clinical courses for PSN⁴⁸: subacute progression in less than 1 month (7%), late acceleration some years after an initial indolent onset (20%), and a very long term insidious,

Table 3 Central nervous system involvement in primary SS: clinical features recently described

Multiple sclerosis-like disease ^{33, 35, 36}
Myelopathy
Acute myelitis ^{37, 38}
Chronic myelopathy ³⁹
Central pontine myelinolysis ⁴⁰
Parkinsonism ⁴¹
Painful tonic/dystonic spasms ⁴²
Bell's palsy ⁴³
Optic neuritis ⁴⁴
CNS vasculitis ⁴⁵
CNS T cell lymphoma ⁴⁶
Cerebral amyloid angiopathy ⁴⁷

Table 4 Sensorineural hearing loss in patients with primary SS: prevalence and immunological markers

	No	Hearing loss	ANA	Anti-Ro/SSA	Anti-La/SSB	aCL
Tumati <i>et al</i> ⁵⁷	30	14 (47)	14 (100)	14 (100)	12 (86)	9 (64)
Ziavra <i>et al</i> ⁵⁸	40	9 (23)	9 (100)	7 (78)	3 (33)	1 (11)
Boki <i>et al</i> ⁵⁹	48	7 (15)	—	—	—	—
Hatzopoulos <i>et al</i> ⁶⁰	22	8 (36)	—	—	—	—
Total	140	38 (27)	23 (100)	21 (91)	15 (65)	10 (43)

Results are shown as No (%).

chronic evolution (73%). Clinically, PSN usually responds poorly to treatment with corticosteroids or immunosuppressive agents, although stabilisation of symptomatology (spontaneously or after treatment) during very long periods is often seen.⁴⁸

AUTONOMIC NEUROPATHY

Several studies have described autonomic disturbances in patients with primary SS, including interstitial cystitis-like symptoms^{49–50} and autonomic cardiovascular abnormalities.^{51–54} Andonopoulos *et al* reported a higher prevalence of autonomic neuropathy in a small series of patients with primary SS, with abnormal responses to cardiovascular tests in 69% and severe autonomic cardiovascular neuropathy in 87.5% of patients, but in none of the healthy controls.⁵¹ In another study, patients with primary SS showed signs of both sympathetic and parasympathetic dysfunction, especially those with anti-Ro/SSA and anti-La/SSB antibodies, and had an abnormal blood pressure reaction to tilt compared with controls.⁵² However, two recent studies have found contrasting results.^{53–54} The small number of patients tested for autonomic disturbances in these studies and the wide variability inherent in autonomic tests does not allow definitive conclusions to be drawn.

MUSCULAR INVOLVEMENT

Two studies have analysed the prevalence and clinical significance of muscular involvement in patients with primary SS, with a predominance of subclinical myositis⁵⁵ rather than other types of myopathies such as inclusion body myositis.⁵⁶ Lindvall *et al* described myalgias in nearly 30% of patients with primary SS, although the causes were diverse, including both non-inflammatory (mainly fibromyalgia) and inflammatory (mainly myositis) processes.⁵⁵ A muscle biopsy was performed in 36 patients, with muscle inflammation being detected in 26 (72%) biopsies. No correlation was found between histological and clinical myositis. This study suggests that subclinical muscle inflammation is often seen in patients with primary SS and that, in nearly 50% of cases, histological evidence of myositis may be detected in asymptomatic patients.

SENSORINEURAL HEARING LOSS

Since 1997, several studies have evaluated hearing loss in primary SS, describing sensorineural hearing loss (SHL) in 38/140 (27%) patients studied^{57–60} (table 4). Some of these studies suggested an association with immunological variables such as antiphospholipid antibodies,⁵⁷ ANA, Ro or La.^{57–59} Boki *et al* found that primary SS is associated with SHL, affecting preferentially the high frequencies,⁵⁹ although clinically significant defects are not common. No specific recommendations have been made on the clinical management of SHL related SS, although a similar approach to that applied in other autoimmune SHL is suggested.⁶¹

Table 5 Haematological abnormalities in patients with primary SS: recent studies

	Prevalence No/total No (%)	References
<i>a) Red blood cell count</i>		
Normocytic anaemia	118/641 (18.4)	5, 62
Haemolytic anaemia	Isolated cases	62, 63
<i>b) White blood cell count</i>		
Leucopenia	116/628 (18.5)	5, 62, 64
Lymphopenia	23/268 (8.6)	62
Neutropenia	19/268 (7.1)	62
Eosinophilia	31/268 (11.6)	62
Chronic agranulocytosis	Isolated cases	62, 63, 65, 66
<i>c) Platelet count</i>		
Thrombocytopenia	55/479 (11.5)	62, 64
<i>d) Other abnormalities</i>		
Raised ESR (>50 mm/1st h)	82/380 (21.6)	62
Hypergammaglobulinaemia	191/585 (32.6)	5, 62, 67
Antiphospholipid antibodies	24/184 (13)	62

HAEMATOLOGICAL ABNORMALITIES

Various studies have emphasised the prevalence and significance of haematological manifestations in patients with primary SS^{5–62–67} (table 5). In a series of 400 patients,⁶² the most common haematological features were cytopenia (33%), raised erythrocyte sedimentation rate (ESR; 22%), and hypergammaglobulinaemia (22%). Although usually asymptomatic, some of these haematological features, such as Coombs's positive haemolytic anaemia,⁶³ agranulocytosis,^{63–66} and thrombocytopenia,⁶³ may present symptoms. Owing to the high prevalence of haematological features in patients with primary SS and the close relationship with the main immunological SS features,⁶² their possible inclusion in a future revision of the current diagnostic criteria, as has happened in SLE, should be considered.

LYMPHOMA

Lymphoma is traditionally considered as the main complication in the natural history of SS, although cross sectional studies have reported that only 98/2311 (4%) patients with primary SS developed lymphoma.⁶² Only one study has prospectively analysed the incidence of lymphoma, which was found in 7/103 (7%) patients with primary SS followed up over 5 years,⁶⁸ while Ioannidis *et al* recorded 38 diagnoses of lymphoma during 4384 person-years of follow up.⁶ The main clinical characteristics of B cell lymphoma in primary SS have been well described in a recent multicentre European study including 33 patients followed up at nine centres.⁶⁹ Lymphadenopathy, skin vasculitis, peripheral nerve involvement, fever, anaemia, and lymphopenia were observed significantly more often than in the general SS population.

Table 6 New therapeutic agents for the treatment of patients with primary SS

	Dose	Number of patients treated	References
<i>Muscarinic agents</i>			
Pilocarpine	5 mg/6 h po	127 (primary + associated SS)	81
	5 mg/12 h po	27 (primary SS)	82
Cevimeline	30 mg/8 h po	25 (primary + associated SS)	83
		62 (primary + associated SS)	84
<i>Biological agents</i>			
Infliximab	3 mg/kg ev	4 (SS associated with RA)	88
		1 (primary SS + neuropathy)	89
		16 (primary SS)	86, 87
		54 (primary SS)	90
Etanercept	5 mg/kg ev	15 (primary SS)	91
Rituximab	25 mg/12 h sc	1 (primary SS + lymphoma)	98
	375 mg/m ² ev	1 (primary SS + lymphoma)	99
IFN α	150 IU/8 h po	300 (primary SS)	94
<i>Other treatments</i>			
Prednisolone	15 mg/d po	20 (primary SS)	101
Octreotide	30 mg im	1 (primary SS)	107
2-Chloro-2'-deoxyadenosine	0.12 mg/kg ev	2 (primary SS + lymphoma)	106
		2 (primary SS + MC)	

B cell lymphoma was primarily located in the marginal zone (49%), with a predominantly extranodal involvement (79%), mainly in the salivary glands (55%). Patients with lymphoma had a significantly worse survival rate, with high to intermediate grade lymphoma, B symptoms (fever, night sweats, and weight loss), and a large tumour diameter (>7 cm) being independent risk factors for death.⁶⁹

EVOLUTION AND OUTCOME

The past 5 years have led to much greater knowledge of the outcome of patients with primary SS. Although not a benign condition, primary SS usually progresses very slowly, with no rapid deterioration in salivary function or dramatic changes in symptoms.⁷⁰ The exceptions to this benign course are the high incidence of lymphoma and the development of extraglandular manifestations, of which two types are found with a differential prognostic significance. A more stable, chronic SS course is usually found in patients with predominantly periepithelial lesions (such as interstitial nephritis, liver or lung disease), while those with predominantly extraepithelial expression (GMN, polyneuropathy, purpura, and vasculitis) present higher morbidity and mortality.⁴⁻⁶ Cryoglobulinaemia probably has a central aetio-pathogenic role in this latter group of patients, contributing to the development of the main extraepithelial manifestations. These features are associated with the highest risk of developing life threatening situations,⁵ with these patients requiring high doses of corticosteroids and immunosuppressive agents and closer monitoring. In contrast, corticosteroids/immunosuppressive agents can be used less frequently in patients with periepithelial lesions, and visits may be scheduled every 6–12 months.

“A major clinical observation has been the discrimination between ‘benign’ and ‘malignant’ primary SS”

In contrast with other autoimmune diseases such as SLE, there is little analytical information on clinical primary SS activity, although several studies have proposed markers such as total serum IgG levels,^{71 72} monoclonal immunoglobulins,⁷³ β_2 -microglobulin,⁷⁴ or BLYS (BAFF).⁷⁵ In addition, various studies have described a close association between extraglandular involvement and positive anti-Ro/La

antibodies,^{3 76 77} suggesting that this subset of patients represents the most active presentation of primary SS.

Few studies have analysed the causes and rates of mortality in patients with primary SS. Skopouli *et al* found that the overall mortality of patients with primary SS increased compared with the general population only in patients with adverse predictors,⁵ whereas Martens *et al* reported an increased mortality in patients with SS associated with other systemic autoimmune diseases, mainly rheumatoid arthritis (RA).⁷⁸ Ioannidis *et al* recorded 39 deaths (seven due to lymphoma) in a cohort of 723 consecutive patients with primary SS, with a standardised mortality ratio of 1.15 compared with the general population of Greece.⁶ These studies suggest that associated processes (vasculitis, other autoimmune diseases, lymphoma) are the main causes of the excess age and sex matched mortality found in patients with SS.

NEW THERAPEUTIC AGENTS

At present, no treatment can modify the evolution of SS. The effects of local treatments such as artificial tears or oral sprays are limited, whereas systemic treatment offers the advantage of dealing with a wider range of symptoms.⁷⁹ New therapeutic approaches include muscarinic agonists and biological agents (table 6).

“Muscarinic agonists and biological agents are new treatments, respectively, for the sicca symptoms and extraglandular features of SS”

Muscarinic agonists

Two muscarinic agonists (pilocarpine and cevimeline) have recently been approved for the treatment of the sicca symptoms of SS. These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function. Clinical studies with pilocarpine (Salagen) tablets in the United States have demonstrated significant subjective and objective benefit for xerostomia and related oral symptoms at doses of 20 mg/day or more.⁸⁰ Vivino *et al* reported that administration of 5 mg pilocarpine tablets four times daily (20 mg/day) was well tolerated and produced significant improvement in sicca symptoms, including dry mouth, dry eyes, and other sicca features.⁸¹

Recently, Tsifetaki *et al* published a 12 week randomised study in which 29 patients with SS were treated with a lower dose of oral pilocarpine (10 mg/day).⁸² Compared with controls, patients receiving pilocarpine showed a significant subjective improvement of dry eyes, with an improvement in the rose bengal test results. No patient discontinued the study because of side effects.

Two recent studies have analysed the use of cevimeline hydrochloride, a cholinergic agent with muscarinic agonist activity prominently affecting the M1 and M3 receptors prevalent in exocrine glands. Fife *et al*, in a double blind, randomised, placebo controlled trial in the United States, reported that treatment with cevimeline, 30 mg three times daily, was well tolerated and provided substantial relief of xerostomia symptoms,⁸³ while Petrone *et al* reported improvement of saliva and tear flow rates, and improvement of subjective sicca symptoms.⁸⁴

Further controlled studies of these muscarinic agonists at different doses are needed in patients with SS, including an individual evaluation of elderly patients or those with comorbid processes, such as cardiovascular, pulmonary, or hepatic diseases.⁸⁵

Biological agents

Recent studies have analysed the role of biological agents for the treatment of primary SS. In a single centre, open label pilot study, Steinfeld *et al* found an improvement in clinical and functional measures in 16 patients with primary SS treated with three infusions of infliximab (3 mg/kg) at 0, 2, and 6 weeks.⁸⁶ In a 1 year follow up study including 10 of these 16 patients, the same authors found a significant decrease in global and local disease manifestations in all 10 patients.⁸⁷ Although treatment was generally well tolerated, the main side effect was a mild, self limiting infusion reaction in four (40%) patients (one of them presenting with

generalised rash, fever, and arthralgia), while two (20%) developed infectious processes (enteritis and tonsillitis). In addition, the main improvement was only observed in subjective symptomatology, with no changes in the ESR or IgG levels. Martin Martin *et al* reported improved salivary secretion in four patients with RA and associated SS treated with infliximab,⁸⁸ while Caroyer *et al* recently reported the successful treatment of a patient with severe sensory neuropathy with infliximab.⁸⁹ However, the results of a multicentre randomised, double blind study of infliximab versus placebo, involving 103 patients with primary SS, clearly showed a lack of efficiency of infliximab in primary SS.⁹⁰ In addition, an uncontrolled study of 15 patients with primary SS treated with etanercept showed no effect on sicca features, glandular function, or histological findings.⁹¹ Anti-tumour necrosis factor agents might have a role in the treatment of specific severe refractory extraglandular features, but in the light of these recent studies, they should not be considered as the first line option for the treatment of primary SS.

Three studies have analysed the safety and efficacy of interferon α (IFN α) in primary SS.^{92–94} Ship *et al* reported improved salivary output and reduced xerostomia, with no significant adverse medical events,⁹² while Shiozawa *et al* reported increased salivary production accompanied by decreased lymphocytic infiltration.⁹³ Recently, Cummins *et al* presented the results of a combined phase III study of 497 patients with primary SS receiving 150 IU of human IFN α versus placebo three times daily by the oromucosal route, with improvement of seven of eight sicca symptoms, although no significant increment of the stimulated whole salivary flow was seen.⁹⁴

A promising treatment for primary SS is rituximab (anti-CD20). CD-20 is considered to be a specific marker for B cells, highly expressed on the surface of pre-B lymphocytes and both residing and activated mature B cells, but not expressed in other cells.⁹⁵ In late 1997, rituximab became the first therapeutic monoclonal agent approved by the FDA for the treatment of B cell lymphoma, and it has been used to treat patients with non-neoplastic autoimmune disorders, such as autoimmune thrombocytopenia, SLE, RA, haemolytic anaemia, and mixed cryoglobulinaemia.⁹⁶ In primary SS, recent reports suggested a role for the treatment of associated lymphoma.^{97–99} The specific target of rituximab (B cells) might suggest a role in modifying the aetiopathogenic events of patients with primary SS, a disease specifically characterised by B cell hyperactivity.

Other treatments

The role of corticosteroids and antimalarial drugs in the treatment of SS is being re-evaluated. Zandbelt *et al* described a patient with SS who underwent salivary gland biopsies before and after treatment with high doses of corticosteroids, and demonstrated an improvement in the main clinical, histological, and immunohistological features after treatment.¹⁰⁰ Miyawaki *et al* treated 20 patients with prednisolone, with a significant decrease in serum IgG, anti-Ro/SSA, anti-La/SSB antibodies, and rheumatoid factor levels and partial decreases of IgA and IgM levels.¹⁰¹ In an experimental study Izumi *et al* found that local corticosteroid irrigation significantly increased the salivary flow rate in patients with SS.¹⁰² However, Tishler *et al* found a significant reduction of some salivary inflammatory markers in patients treated with 200 mg/day hydroxychloroquine,¹⁰³ which has previously been shown to be effective for treating SS related arthralgias, myalgias, and asthenia.^{104–105} Finally, several studies performed in small series of patients have analysed the efficacy of other therapeutic agents, including 2-chloro-2'-deoxyadenosine, octreotide, AZT, or azathioprine.^{106–109}

Table 7 Current concepts in the extraglandular expression of primary SS

a) Cutaneous involvement

Prognostic significance of cryoglobulinaemia and cutaneous purpura^{4–6}
Ro associated, polycyclic, photosensitive lesions (SCLÉ-like)^{4, 7, 8}

b) Pulmonary involvement

High frequency of bronchial/bronchiolar disease (30–50%)^{18–20}
Insidious and slow progression of pulmonary disease²³

c) Renal involvement

Indolent subclinical course of TIN³⁰
Demonstration of glomerulonephritis in 44% of patients biopsied^{29, 30}
Key role of cryoglobulinaemia in SS related glomerulonephritis^{29, 30}

d) Neurological involvement

Increased cerebral white matter lesions³³
Long term insidious course and poor response to treatment of PSN⁴⁸
Autonomic disturbances (abnormal responses to cardiovascular tests)^{151–54}

e) Lymphoproliferative involvement

Prevalence of 4% of lymphoma in cross sectional studies⁶²
Lymphadenopathy, purpura, and neuropathy as clinical markers of lymphoproliferation⁶⁹
Anaemia, lymphopenia, cryoglobulins, and mlg as analytical markers⁶⁹
Salivary glands as the main site of lymphoma⁶⁹
Higher prevalence of extranodal involvement⁶⁹

f) Miscellaneous

Subclinical muscle inflammation⁵³
Interstitial cystitis associated with severe urological symptoms^{49, 50}
Sensorineural hearing loss in nearly 25% of patients^{57–60}
Rare occurrence of symptomatic cytopenias^{62, 63, 66}
Autoimmune myocarditis^{110, 111}
Fatigue^{112–116}

CONCLUSION

The increasing amount of published information on primary SS has contributed to a better understanding of the extraglandular expression of the disease and has changed the therapeutic management of these patients. A wide spectrum of extraglandular features has been studied in the past 5 years (table 7), and understanding of the involvement of some organs and systems has been expanded. Substantially more information on the outcome of patients with primary SS is now available, which indicates that patients with a predominantly extraepithelial expression (often associated with cryoglobulinaemia) should be monitored and managed differently from patients with a predominantly periepithelial or sicca limited disease. The therapeutic management of patients with primary SS in coming years will be based on muscarinic agonists for sicca features and a key role for immunosuppressive/biological agents in the treatment of extraglandular features.

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